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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,280	03/08/2005	Peter Bernstein	133087.12101(100829-1PUS)	3799

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EXAMINER	
O'DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
03/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,280	BERNSTEIN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 14-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 14-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-9, 12-13 are pending in the current application.

2. This application is a 371 of PCT/SE03/01399 filed 09/08/2003, which claims priority to the following Swedish applications: 0202674-8 filed 09/09/2002 and 0301052-7 filed 04/08/2003.

Response to Arguments

3. Applicant's arguments filed February 5, 2008 have been fully considered but they are not fully persuasive. The rejections of claims 7, 9-13 are withdrawn since they have in fact been canceled. The written description rejection for "in-vivo hydrolysable precursor" is withdrawn since this language has been removed from the claims. The rejection under 35 U.S.C. 103 (a) for obviousness is maintained. The applicant has argued that Harrison has some deficiencies with regard to the teaching of naphthyl. The examiner disagrees, as one of ordinary skill would recognize the lipophilicity of naphthyl as being similar to the various phenyl groups of Harrison, and recognize their interchangability. The applicant has argued that Harrison doesn't suggest anything about the lipophilicity, however this is incorrect. Nearly all of his compounds bear greasy groups, including CF3, phenyl, t-butyl, bromine etc. Hagiwara was sufficient to show the art recognized equivalence, however in order to buttress the examiner's conclusion and show that the examiner is not taking official notice, the examiner submits that Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773, clearly teaches the exact modification (down to the very precise substituents on the naphthyl ring), thus the use of naphthyl in these NK1-antagonists and the substitution of naphthyl for phenyl was very well known even in this very small field. Starting

with the known selective antagonist SR48968, Bernstein modified the phenyl portion by screening a diverse set of compounds where the phenyl was replaced with "over 100 aryl, heteroaryl and arylalkyl groups". In the words of Bernstein the result of this study was "the most potent, dual acting compound to come out of this array was the naphthamide **2a**". Bernstein goes on to describe that "to follow-up the discovery of this naphthamide we explored the effect of substituents on the naphthalene ring." It is interesting that 3-cyano-naphthyl was the preferred substituent, as in compound **4**. This 3-cyano naphthyl group is also the preferred substituent of the instant case and is what distinguishes these compounds from those of Harrison et. al. There can be no doubt that this was the preferred substituent.

The examiner maintains the 112 1st paragraph rejections for enablement, since the assays presented (ligand binging assays) do not correlate with disease treatment. The applicant has argued in terms of the success of certain clinical trials with other compounds, however the key issue here is the correlation between the assay presented and treatment of a disease. No such correlation exists. The real problem here is that the NK-1 receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor……**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation…… Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**."

Here we have exactly this situation, namely a ligand with affinity, but no known function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." The applicant is arguing that since the compounds have the utility binding the receptor (as clearly discussed in Kenakin), that they are automatically enabled for the treatment of diseases. The examiner agrees that any compound that binds a GPCR may eventually have a therapeutic use, which is why a utility rejection was not made in the last office action. Of course all therapeutically effective compounds have affinity for their respective targets, but it is specious logic that leads one to the converse that all active compounds are therapeutically useful. Consider fluphenazine an approved drug for the treatment of psychotic disorders, which binds to the 5-HT6 receptor. LSD also binds the 5-HT6 receptor. If the reasoning put forth by the applicant holds true then LSD should be used to treat psychotics, however I think no medical doctor would suggest that LSD be given to psychotics. The point Kenakin is trying to make is that binding is the first step to discovering a drug, and that just because a compound may be a weak agonist or antagonist or perhaps neither this does not preclude its potential for therapeutic utility because GPCRs are not to be viewed as G-protein switches. It is undue experimentation to take a compound that has the data revealed in the specification and extrapolate these results into complex diseases. Clearly the examiner showed this very unpredictability with the references cited showing negative clinical trials with compounds that have receptor affinity in cell based assays. The arguments of counsel are not probative and do not take the place of evidence. The double patenting rejection is maintained as for the reasons of record. This action is made **FINAL**.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

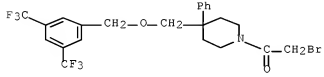
4. Claims 1-6, are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et. al. WO 94/110165, cited on the IDS in view of Hagiwara et. al. "Studies on Neurokinin Antagonists. 4. Synthesis and Structure-Activity Relationships of Novel Dipeptide Substance P Antagonists: N^2-[(4R)-4-Hydroxy-l(-[l -methyl-1H-indol-3-yl)carbonyl]-L-prolyl]-N-methyl- N-(phenylmethyl)-3-(2-naphthyl)-L-alaninamide and Its Related Compounds" *Journal of Medicinal Chemistry* **1994**, *37*, 2090-2099 OR Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

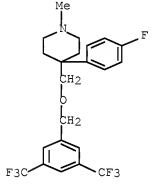
(MPEP 2141.01)

Harrison et. al. teaches NK-1 antagonists that are analogs of the compounds of the instant case that have the same utility. In particular the hundred or so compounds below:

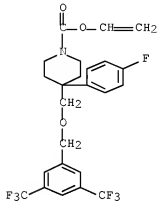
RN 160376-77-2 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(bromoacetyl)-4-phenyl- (9CI) (CA INDEX NAME)



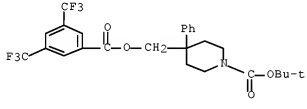
RN 160376-80-7 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(4-fluorophenyl)-1-methyl- (9CI) (CA INDEX NAME)



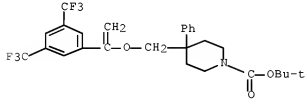
RN 160376-81-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(4-fluorophenyl)-, ethenyl ester (9CI) (CA INDEX NAME)



RN 160376-85-2 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[[3,5-
bis(trifluoromethyl)benzoyl]oxy]meth
yl]-4-phenyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



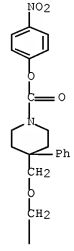
RN 160376-86-3 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[[1-[3,5-
bis(trifluoromethyl)phenyl]etheny
l]oxy]methyl]-4-phenyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



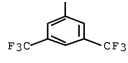
RN 160376-90-9 CAPLUS

CN 1-Piperidinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-, 4-nitrophenyl ester (9CI) (CA INDEX NAME)

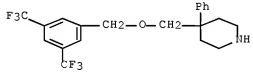
PAGE 1-A



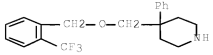
PAGE 2-A



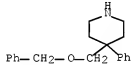
RN 160375-92-8 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-
(9CI) (CA INDEX NAME)



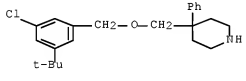
RN 160375-94-0 CAPLUS
CN Piperidine, 4-phenyl-4-[[[2-(trifluoromethyl)phenyl]methoxy]methyl]-(9CI)
(CA INDEX NAME)



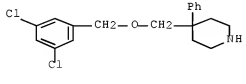
RN 160375-95-1 CAPLUS
CN Piperidine, 4-phenyl-4-[(phenylmethoxy)methyl]- (9CI) (CA INDEX NAME)



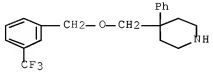
RN 160375-96-2 CAPLUS
CN Piperidine, 4-[[[3-chloro-5-(1,1-dimethylethyl)phenyl]methoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)



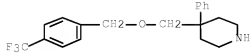
RN 160375-97-3 CAPLUS
CN Piperidine, 4-[[(3,5-dichlorophenyl)methoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)



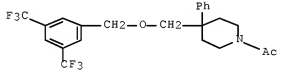
RN 160375-98-4 CAPLUS
CN Piperidine, 4-phenyl-4-[[[3-(trifluoromethyl)phenyl]methoxy]methyl]-(9CI)
(CA INDEX NAME)



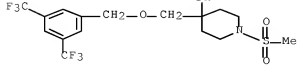
RN 160375-99-5 CAPLUS
CN Piperidine, 4-phenyl-4-[[[4-(trifluoromethyl)phenyl]methoxy]methyl]-
(9CI)
(CA INDEX NAME)



RN 160376-00-1 CAPLUS
CN Piperidine, 1-acetyl-4-[[[3,5-
bis(trifluoromethyl)phenyl]methoxy]methyl]-4-
phenyl- (9CI) (CA INDEX NAME)



RN 160376-01-2 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-
(methylsulfonyl)-4-phenyl- (9CI) (CA INDEX NAME)



RN 160376-08-9 CAPLUS
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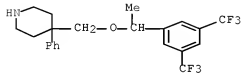
phenyl-
(9CI) (CA INDEX NAME)



RN 160376-09-0 CAPLUS
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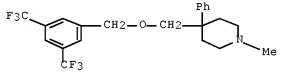
phenyl- (9CI) (CA INDEX NAME)



RN 160376-10-3 CAPLUS
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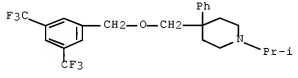

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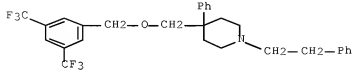
(2-phenylethyl)- (9CI) (CA INDEX NAME)



RN 160376-12-5 CAPLUS
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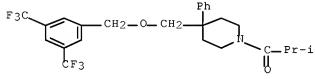

RN 160376-13-6 CAPLUS
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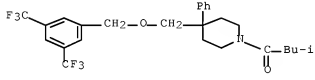

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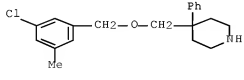

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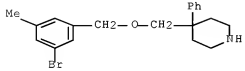

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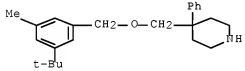
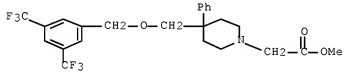
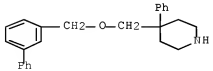
CN Piperidine, 4-[[[3-(1,1-dimethylethyl)-5-methylphenyl]methoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)



RN 160376-18-1 CAPLUS
CN 1-Piperidineacetic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-, methyl ester (9CI) (CA INDEX NAME)

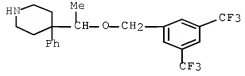


RN 160376-27-2 CAPLUS
CN Piperidine, 4-[([1,1'-biphenyl]-3-ylmethoxy)methyl]-4-phenyl- (9CI) (CA INDEX NAME)

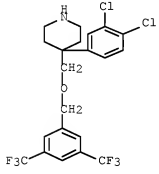


RN 160376-30-7 CAPLUS
CN Piperidine, 4-[1-[[3,5-bis(trifluoromethyl)phenyl]methoxy]ethyl]-4-phenyl-

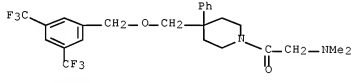
(9CI) (CA INDEX NAME)



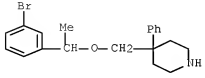
RN 160376-31-8 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(3,4-dichlorophenyl)- (9CI) (CA INDEX NAME)



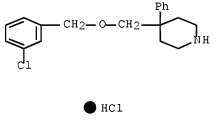
RN 160376-39-6 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-[(dimethylamino)acetyl]-4-phenyl- (9CI) (CA INDEX NAME)



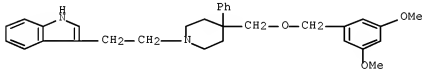
RN 160376-44-3 CAPLUS
CN Piperidine, 4-[[1-(3-bromophenyl)ethoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



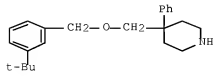
RN 160376-47-6 CAPLUS
CN Piperidine, 4-[[(3-chlorophenyl)methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



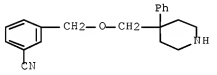
RN 160376-51-2 CAPLUS
CN 1H-Indole, 3-[2-[4-[[(3,5-dimethoxyphenyl)methoxy]methyl]-4-phenyl-1-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)



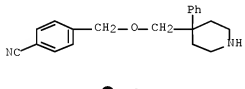
RN 160376-53-4 CAPLUS
CN Piperidine, 4-[[[3-(1,1-dimethylethyl)phenyl]methoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)



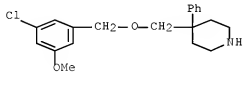
RN 160376-54-5 CAPLUS
CN Benzonitrile, 3-[[(4-phenyl-4-piperidinyl)methoxy]methyl]- (9CI) (CA INDEX NAME)



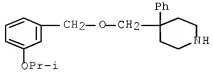
RN 160376-56-7 CAPLUS
CN Benzonitrile, 4-[[(4-phenyl-4-piperidinyl)methoxy]methyl]-, monohydrochloride (9CI) (CA INDEX NAME)



RN 160376-61-4 CAPLUS
CN Piperidine, 4-[[(3-chloro-5-methoxyphenyl)methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)

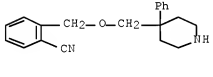


RN 160376-66-9 CAPLUS
CN Piperidine, 4-[[[3-(1-methylethoxy)phenyl]methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



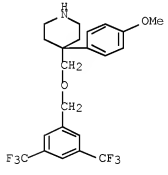
● HCl

CN Benzonitrile, 2-[[(4-phenyl-4-piperidinyl)methoxy]methyl]-, monohydrochloride (9CI) (CA INDEX NAME)



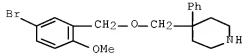
● HCl

RN 160376-69-2 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(4-methoxyphenyl)-, hydrochloride (9CI) (CA INDEX NAME)

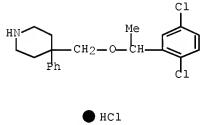


● HCl

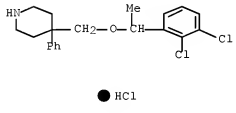
RN 160376-70-5 CAPLUS
CN Piperidine, 4-[[(5-bromo-2-methoxyphenyl)methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



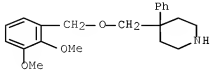
RN 160376-71-6 CAPLUS
CN Piperidine, 4-[[1-(2,5-dichlorophenyl)ethoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



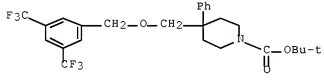
RN 160376-72-7 CAPLUS
CN Piperidine, 4-[[1-(2,3-dichlorophenyl)ethoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



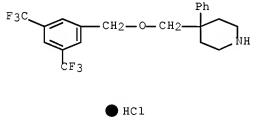
RN 160376-73-8 CAPLUS
CN Piperidine, 4-[[(2,3-dimethoxyphenyl)methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



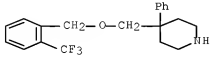
RN 160376-91-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]m
ethyl]-4-phenyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 160376-92-1 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-,
hydrochloride (9CI) (CA INDEX NAME)

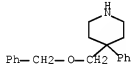


RN 160376-94-3 CAPLUS
CN Piperidine, 4-phenyl-4-[[[2-(trifluoromethyl)phenyl]methoxy]methyl]-,
hydrochloride (9CI) (CA INDEX NAME)



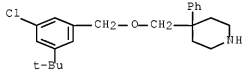
● HCl

RN 160376-95-4 CAPLUS
CN Piperidine, 4-phenyl-4-[(phenylmethoxy)methyl]-, hydrochloride (9CI) (CA
INDEX NAME)



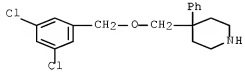
● HCl

RN 160376-96-5 CAPLUS
CN Piperidine, 4-[[[3-chloro-5-(1,1-dimethylethyl)phenyl]methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)

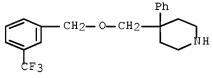


● HCl

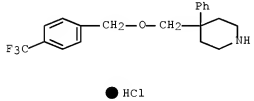
RN 160376-97-6 CAPLUS
CN Piperidine, 4-[[(3,5-dichlorophenyl)methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



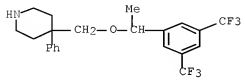
RN 160376-98-7 CAPLUS
CN Piperidine, 4-phenyl-4-[[[3-(trifluoromethyl)phenyl]methoxy]methyl]-, hydrochloride (9CI) (CA INDEX NAME)



RN 160376-99-8 CAPLUS
CN Piperidine, 4-phenyl-4-[[[4-(trifluoromethyl)phenyl]methoxy]methyl]-, hydrochloride (9CI) (CA INDEX NAME)



RN 160377-03-7 CAPLUS
CN Piperidine, 4-[[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]methyl]-4-phenyl-
, hydrochloride (9CI) (CA INDEX NAME)

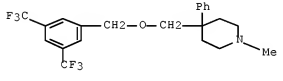


● HCl

RN 160377-04-8 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-methyl-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

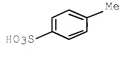
CM 1

CRN 160376-09-0
CMF C22 H23 F6 N O



CM 2

CRN 104-15-4
CMF C7 H8 O3 S

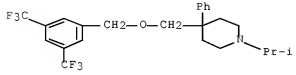


RN 160377-05-9 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(1-methylethyl)-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

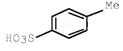
CRN 160376-10-3

CMF C24 H27 F6 N O



CM 2

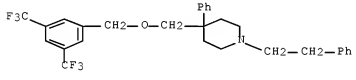
CRN 104-15-4
CMF C7 H8 O3 S



RN 160377-06-0 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-4-phenyl-1-
(2-phenylethyl)-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

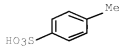
CM 1

CRN 160376-11-4
CMF C29 H29 F6 N O



CM 2

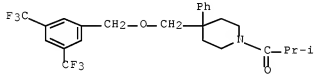
CRN 104-15-4
CMF C7 H8 O3 S



RN 160377-07-1 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(2-methyl-1-oxopropyl)-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

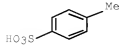
CM 1

CRN 160376-12-5
CMF C25 H27 F6 N O2



CM 2

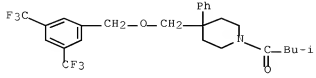
CRN 104-15-4
CMF C7 H8 O3 S



RN 160377-08-2 CAPLUS
CN Piperidine, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1-(3-methyl-1-oxobutyl)-4-phenyl-, 4-methylbenzenesulfonate (9CI) (CA INDEX NAME)

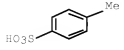
CM 1

CRN 160376-13-6
CMF C26 H29 F6 N O2

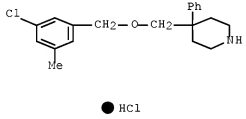


CM 2

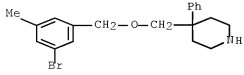
CRN 104-15-4
CMF C7 H8 O3 S



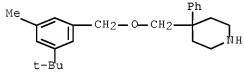
RN 160377-09-3 CAPLUS
CN Piperidine, 4-[[(3-chloro-5-methylphenyl)methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



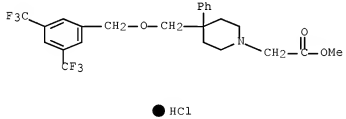
RN 160377-10-6 CAPLUS
CN Piperidine, 4-[[(3-bromo-5-methylphenyl)methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



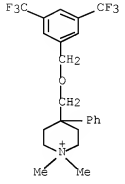
RN 160377-11-7 CAPLUS
CN Piperidine, 4-[[[3-(1,1-dimethylethyl)-5-methylphenyl]methoxy]methyl]-4-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



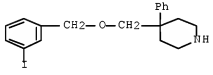
RN 160377-12-8 CAPLUS
CN 1-Piperidineacetic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methy l]-4-phenyl-, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



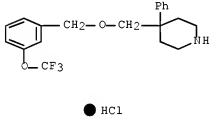
RN 160377-13-9 CAPLUS
CN Piperidinium, 4-[[[3,5-bis(trifluoromethyl)phenyl]methoxy]methyl]-1,1-dimethyl-4-phenyl-, iodide (9CI) (CA INDEX NAME)



RN 160377-34-4 CAPLUS
CN Piperidine, 4-[[(3-iodophenyl)methoxy]methyl]-4-phenyl- (9CI) (CA INDEX NAME)



RN 160377-37-7 CAPLUS
CN Piperidine, 4-phenyl-4-[[[3-(trifluoromethoxy)phenyl]methoxy]methyl]-, hydrochloride (9CI) (CA INDEX NAME)



Hagiwara et. al. teach Nk-1 antagonists bearing both phenyl and naphthyl moieties and did extensive SAR studies, and came to the following conclusion about the substitution of phenyl for naphthyl:

"As shown in the previous paper,[13] an aromatic functionality such as a L-phenylalanine is essential in this part. We therefore limited the modifications of this part to substituted L-phenylalanines or bicyclic aromatic L-amino acids. Electronic and lipophilic features of the substituent tend not to influence the binding activity, and some of bicyclic aromatic α amino acids including an L-2-naphthylalanine **(7k)** had potent binding activity. Regarding oral absorption, increasing lipophilicity such as introduction of a trifluoromethyl **(78)** or an L-2-naphthylalanine **(7k)** tends to enhance the activity. These facts imply that this class of compounds is absorbed through the lipid bilayer on the digestive tracts by a simple diffusion mechanism."

While not remarkably similar in structure, the compounds of Hagiwara teach that in the field of NK-1 receptor antagonists a substitution of naphthyl for phenyl is routine and desirable.

In order to buttress the examiner's conclusion and show that the examiner is not taking official notice, the examiner submits that Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773, clearly teaches the exact modification (down to the very precise substituents on the naphthyl ring), thus the use of naphthyl in these NK1-antagonists and the substitution of naphthyl for phenyl was very well known even in this very small field. Starting with the known selective antagonist SR48968, Bernstein modified the phenyl portion by screening a diverse set of compounds where the phenyl was replaced with "over 100 aryl, heteroaryl and arylalkyl groups". In the words of Bernstein the result of this study was "the most potent, dual acting compound to come out of this array was the naphthamide 2a". Bernstein goes on to describe that "to follow-up the discovery of this naphthamide we explored the effect of substituents on the naphthalene ring." It is interesting that 3-cyano-naphthyl was the preferred substituent of the instant case. This 3-cyano naphthyl group is also the preferred substituent of the instant case and is what distinguishes these compounds from those of Stevenson et. al. There can be no doubt that this was the preferred substituent.

Ascertainment of the difference between the prior art and the claims

The instant claims differ from the compounds of Harrison et. al only in the substitution of a naphthyl group for the phenyl of the Harrison et. al. Hagiwara does not teach the compounds of the instant case, but rather show the change made to compounds of Harrison et. al. to be routine, equivalent to the phenyl of Harrison and desirable in this very narrow field of NK-1 receptor antagonists.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Harrison et. al. to produce the instant invention. Analogs differing only in the substitution of phenyl for naphthyl, are *prima facie* obvious, and require no secondary teaching when the utility is the same. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to replace phenyl with naphthyl. Harrison suggests that lipophilicity of the aryl moiety to be important since numerous compounds bearing the lipophilic CF3 group were prepared, thus naphthyl being slightly more lipophilic would have increased potency. Moreover Hagiwara, shows the equivalence of phenyl and naphthyl, and desirability of this change which increases the lipophilicity of NK-1 antagonists which in turn increases bioavailability without altering binding, which would be a strong motiviation to make the invention of the instant claims. Naphthyl and more specifically, the 3-cyano naphthyl group is also the preferred substituent of Bernstein et. al. who showed the preference for naphthyl over phenyl. There can be no doubt that this was the preferred substituent.

Ex parte WESTFAHL, 136 USPQ 265 (Bd. Pat. App. & Int. 1962):

> "Appellant relies upon the case of In re Jones, 32 CCPA 1020, 1945 C.D. 304, 579 O.G. 148, 149 F.2d 501, 65 USPQ 480 , as supporting the patentability of claim 8 because in that case a naphthyl compound was held to be patentable over the corresponding phenyl compound. However, the rejection in that case was based upon the premise, held to be untenable by the court, that benzene and naphthalene are members of a homologous series. In the present case, **the examiner does not rely upon any theory of homology but has cited a reference (Richter II) teaching that naphthalene is very similar to benzene and forms a series of analogous derivatives**."

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8, 14-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Disclosure of the activity of the compounds and dosages that are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The only information given as to what these compounds may do, at least in the pharmacological sense, is on pg. 16 of the disclosure

> Compound A of the present invention had a Ki of about 2 nM in Test A and an IC_{50} of about 12 nM in Test B.

One cannot predict a priori what the outcome of such complex pharmacological behavior would be in the complex diseases of claim 8 (it is not clear what diseases are being treated in claim 8). The inventor has provided no working examples of the treatment of a disease, and the assays given do not correlate with disease treatment. This receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor……**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor**

ensemble [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, **this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation**..... "

Here we have exactly this situation, namely a ligand with affinity, but limited information about its function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility."

The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). In regard to claim 12 & 13, depression is the only disease where such treatment might be efficacious, however this is debatable as stated in a recent review (Rosenzwieg-Lipson et. al. Pharmacology & Therapeutics 2007, 113, 134-153) pg. 140 paragraph 3 sentence 2:

> "Although the NK-1 antagonist aprepitant was not proven efficacious in Phase III depression trials (Keller et al., 2006), it is conceivable that the combination of aprepitant with an SSRI might result in rapid onset of antidepressant effects. To this end, NK-1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies (Guiard et al., 2004). Whether this combination or other non-monoaminergic mechanisms will produce rapid onset antidepressant effects remains to be answered."

Thus the state of the art in the area of these dual antagonists is murky at best. Moreover, even if these compounds were evaluated simply as NK-1 antagonists (which it is unclear if they actually are), a recent review article (McLean, S. *Current Pharmaceutical Design* **2005**, *11*, 1529, pg. 1542 paragraph 3) states, that:

> "In summary, clinical studies with three different compounds demonstrate antidepressant efficacy in both mildly depressed as well as melancholic patients. Furthermore, the favorable side effect profile of the agents suggests a viable therapy particularly for people experiencing significant sexual side effects with currently available antidepressants. **This has to be balanced against a number of trials in which NK1 receptor antagonists failed to show activity. In addition to the previously mentioned negative trials, NKP608 another NK1 receptor antagonist was reported on the Novartis web site to have been terminated from further development for depression although it is unclear whether this was due to side effects or lack of efficacy. To date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies."**

It seems very unlikely that one skilled in the art (a Medical Doctor or Pharmacist) would know what to do with these compounds. The other exhaustive list of diseases such as whatever is encompassed by claim 8 have no credibility for treatment given the mechanism that applicant alleges and the current knowledge in the art. The factors outlined in In re Wands mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to use"...."the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

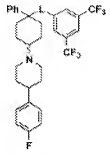
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-6, 8, 14-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/539,140 in view of Elliot et. al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758.

This is a provisional obviousness-type double patenting rejection. The instant claims differ from those of the '140 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists.

"Table 1 summarises the effect of modifications to the amide linker of 2. Throughout, trans-isomers have higher affinity than the corresponding cis-isomers. **A number of different linkers are tolerated, most notably the amides 2 and 15, the amine 17 and ether 23.** The relatively poor affinity of the propyl linker 24 (hNK_1 IC_{50} 40nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor." Pg. 1756-1757 Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758

Table 1. Linker replacements



Compd	-L-	Stereochemistry	hNK$_1$ IC$_{50}$ (nM)[a]
11		*cis*-	150 ± 80
2		*trans*-	0.34 ± 0.10
12		*cis*-	250 ± 26
13		*trans*-	6.3 ± 2.5
14		*cis*-	85 ± 46
15		*trans*-	0.70 ± 0.44
16		*cis*-	82 ± 0
17		*trans*-	1.7 ± 0.6
18		*cis*-	140 ± 49
19		*trans*-	2.5 ± 0.6
20		*cis*-	50% @ 1000
21		*trans*-	120 ± 99
22		*cis*-	59 ± 18
23		*trans*-	4.2 ± 1.9
24		1:1 *cis*- and *trans*-	40 ± 3

[a]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean ± SD ($n = 3$).[5]

11. Claims 1-6, 8, 14-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending

Application No. 10/525,303. The claims are coextensive in scope. in view of Elliot et. al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758.

This is a provisional obviousness-type double patenting rejection. The instant claims differ from those of the '303 application by the identity of the moiety linking the naphthyl ring to the piperidine. This change is taught by Elliot et. al. in his NK-1 antagonists.

"Table 1 summarises the effect of modifications to the amide linker of 2. Throughout, trans-isomers have higher affinity than the corresponding cis-isomers. **A number of different linkers are tolerated, most notably the amides 2 and 15, the amine 17 and ether 23.** The relatively poor affinity of the propyl linker 24 (hNK_1 IC_{50} 40nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor." Pg. 1756-1757 Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758

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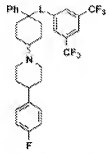

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11		*cis*-	150 ± 80
2		*trans*-	0.34 ± 0.10
12		*cis*-	250 ± 26
13		*trans*-	6.3 ± 2.5
14		*cis*-	85 ± 46
15		*trans*-	0.70 ± 0.44
16		*cis*-	82 ± 0
17		*trans*-	1.7 ± 0.6
18		*cis*-	140 ± 49
19		*trans*-	2.5 ± 0.6
20		*cis*-	50% @ 1000
21		*trans*-	120 ± 99
22		*cis*-	59 ± 18
23		*trans*-	4.2 ± 1.9
24		1:1 *cis*- and *trans*-	40 ± 3

[a]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean ± SD ($n = 3$).[5]

This is a provisional obviousness-type double patenting rejection.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625